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Applied Biosystems: Celebrating 25 Years of Advancing Science

by Mark Springer

This month, **Applied Biosystems** (Foster City, CA) celebrates 25 years of advancing science. Throughout its history, the company has been a partner in discovery with scientists. By supplying researchers and technicians with a steady stream of technologies, the company has both enabled landmark scientific discoveries and helped to transform those discoveries into practical research and industry applications. A timeline of milestones in the company's history intertwines with life science research breakthroughs achieved over the past quarter century. Looking to the future, **Applied Biosystems** remains committed to providing scientists and customers with technology solutions that transition their discoveries from the research laboratory through validation and finally to a clinical setting.

"Our technologies empower our customers to make discoveries and products that change lives," says Catherine Burzik, President of **Applied Biosystems**. "Partnering with scientists, clinicians, and researchers worldwide, we literally make a difference in improving the human condition. That's tremendously exciting and satisfying."

Founded in May of 1981 by Andre Marion and Sam Eletr, Ph.D. (Figure 1), two engineers from **Hewlett-Packard Co.** (Palo Alto, CA), **Applied Biosystems** began operations in Foster City, CA, with a mission to develop, manufacture, and market reagents and automated instruments for life science research and diagnostic applications.

The company developed and manufactured the first of its many innovative tools for use in the life sciences when it introduced the model 470A protein sequencer, equipping scientists with an automated system capable of determining the amino acid sequence of a protein. This advance in protein sequencing made it possible for scientists to correlate protein sequence with its activity and function.



Figure 1 Andre F. Marion and Sam H. Eletr, Ph.D.

In 1983, Mike Hunkapiller, Ph.D., joined **Applied Biosystems**. In his 21 years with the company, Dr. Hunkapiller held many positions, most recently as President and General Manager, before he retired in 2004. During his years with the company, Dr. Hunkapiller helped to grow the company from a startup to an almost \$2 billion-a-year supplier of systems, reagents, and technologies for the life sciences. In 1986, **Applied Biosystems** released the 370A, its first commercially available four-color fluorescence automated DNA sequencer. This milestone marked the beginning of an ongoing commitment by the company to evolve its DNA sequencing chemistries and systems to meet the increasing demands of the scientific community for higher-throughput, more sophisticated DNA sequencing solutions.

The 370A was followed four years later by the release of the ABI PRISM[®] 373 DNA sequencer. Then, in 1995, the company released the ABI PRISM 377 DNA sequencer, an automated DNA sequencer that provided a four- to fivefold increase in throughput compared with that of the 373 system. Both of these slab-gel electrophoresis systems were based on the company's patented four-color fluorescent dye chemistry.

In 1986, LC-MS technology was being adopted by life science researchers to improve the analysis of biological samples. At that time, a joint venture, now called **Applied Biosystems/MDS SCIEX**, was formed. As part of this joint venture, **Applied Biosystems** developed sophisticated systems to automate LC-MS and LC-MS-MS technology.

According to Laura Lauman, Division President, Proteomics and Small Molecules, **Applied Biosystems**, "Throughout its history, **Applied Biosystems** and **Applied Biosystems/MDS SCIEX** have developed, manufactured, and marketed mass spectrometry systems. Applications of our systems have accelerated the drug discovery and development process by making it possible for researchers to identify and quantitate potential drug candidates and biomarkers associated with human disease."

Also in the 1980s, Kary Mullis of **Cetus Corp.** developed a reliable, rapid method for amplifying small quantities of DNA that became known as the polymerase chain reaction (PCR). In 1987, only a few years after the discovery of the PCR technique, the first commercial PCR enzyme and thermal cycler systems became widely accessible to scientists. Use of the PCR and automation of the technique by systems have made possible some of the greatest discoveries in biology over the past quarter century.

By 1988, **Applied Biosystems** was manufacturing more than 25 different automated instruments; over 400 liquid chromatography columns and components; and over 300 reagents and consumables for the synthesis, purification, and analysis of DNA, proteins, and other biological molecules. The company's products were regularly being used by scientists to identify the mutations responsible for the more than 4000 known human genetic diseases as well as those mutations that contributed to various forms of cancer. Diagnostic tests were now available for cystic fibrosis, sickle cell anemia, Duchenne muscular dystrophy, and hemophilia.

The 1995 release of the ABI PRISM 310 genetic analyzer represented a breakthrough in DNA sequencing technology. The 310 system was based on a novel polymer chemistry that allowed automated DNA sequencing through a single capillary. The introduction of capillary electrophoresis technology made it possible for researchers to sequence DNA without enduring the tedious process of loading gels. Just a few years later, capillary electrophoresis would become the cornerstone technology of **Applied Biosystems**' most successful DNA sequencers, the 96-capillary high-throughput ABI PRISM 3700

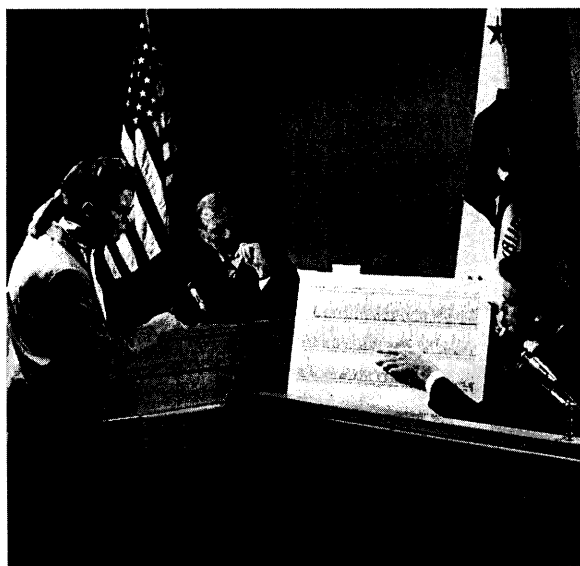


Figure 2 In the 1990s, DNA analysis became a powerful tool in the courtroom for human identification.

DNA analyzer and ABI PRISM 3100 genetic analyzer. Both of these instruments were built in cooperation with **Hitachi Corp.** (Tokyo, Japan).

In the 1990s, many laboratories began using fluorescent dye chemistry to label the DNA bases. **Applied Biosystems** manufactured and supplied fluorescent dye reagents in a number of different sequencing chemistry kits. In 1998, the company introduced its BigDye[®] terminator cycle sequencing kits, which greatly improved scientists' ability to perform DNA sequencing on automated instruments.

The 1990s also saw the emergence of forensic DNA analysis, examination of the length variation of DNA repeat sequences to identify individuals. Today, DNA fingerprinting technology continues to gain widespread acceptance as a reliable method of identifying individuals who are involved in criminal investigations, are victims of disasters, or are subjects of paternity testing. In 1999, the company set a new standard for forensic human identification with the release of both the AmpFLSTR[®] Profiler Plus[®] PCR amplification kit and the AmpFLSTR COfiler[®] PCR amplification kit, short tandem repeat (STR)-based kits used extensively today by forensic scientists for DNA analysis applications (Figure 2).

Throughout the 1990s, scientists witnessed steady advances in mass spectrometry that led to enhanced approaches to protein identification and characterization. For example, time-of-flight (TOF) MS with matrix-assisted laser desorption ionization (MALDI) became an important technique for understanding

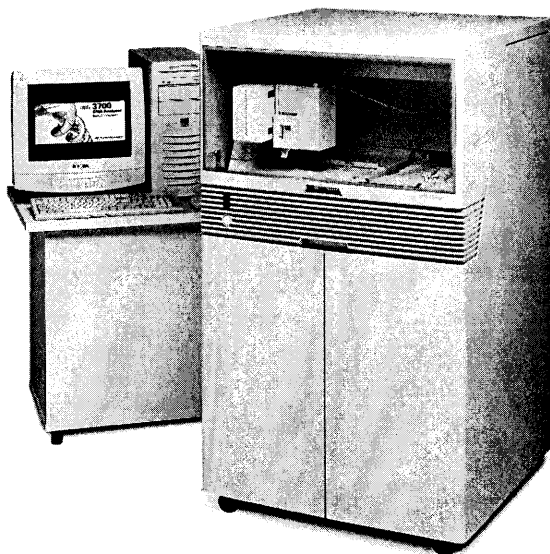


Figure 3 ABI PRISM 3700 DNA analyzer.

large biomolecules, including proteins. **Applied Biosystems** gained this technology when it acquired **PerSeptive Biosystems** in 1997.

In 1995, **Applied Biosystems**, at the time a division of the **Perkin-Elmer Corp.**, welcomed Tony White as the new CEO of the company. Mr. White currently serves as CEO of **Applera Corp.**, the parent company of **Applied Biosystems**.

In 1996, **Applied Biosystems** introduced the world to real-time PCR with the release of the ABI PRISM 7700 sequence detection system. About this time, TaqMan[®] assay chemistry, a PCR analysis technique used with this system for measuring gene expression, was also developed with strategic partner **Roche Molecular Systems** (Alameda, CA). Used in conjunction with TaqMan assay chemistry, the 7700 system detects the presence of genetic mutations or the amount of mRNA made from an active gene. Scientists have used real-time PCR assays to evaluate the amount of HIV virus in an infected patient and to detect levels of expression of various cancer-related or other significant genes.

Released in 1999, the 3700 DNA analyzer (Figure 3) accelerated the sequencing of the human genome ahead of schedule by almost five years. In the year 2000, powered by a fleet of 3700 systems, the Human Genome Project (HGP) and **Celera Genomics** (Rockville, MD) independently completed their drafts of the human genome. In February 2001, **Celera Genomics** published its results in *Science*, and the HGP published its results in *Nature*.

At the turn of the century, mass spectrometry continued to expand the capabilities of scientists in proteomic and drug development efforts. In 1999, **Applied Biosystems/MDS SCIEX** introduced the QSTAR[®] hybrid LC-MS-MS system, its first mass spectrometer for protein and drug discovery and development. The following year, the oMALDI ion source enabled the API QSTAR Pulsar hybrid LC-MS-MS system to easily switch between atmospheric pressure ionization (API), nanospray, and MALDI sources for increased throughput of protein and peptide samples. Also, ICAT[®] reagents and software offered researchers a revolutionary approach to high-volume protein quantification and expression studies, including the identification of low-abundant proteins by mass spectrometry without 2-D gels.

With the completion of the human genome, many researchers turned their attention to proteomics and the challenge of high-throughput methods for characterizing the multitude of different proteins in the body. To meet this challenge, **Applied Biosystems/MDS SCIEX** introduced the 4800 MALDI TOF/TOF analyzers in 2001. This system was developed specifically for the growing field of proteomics.

Applied Biosystems technology was used to help with the aftermath of the tragedies of September 11, 2001. The company's human identification technology was used extensively in New York City to identify World Trade Center victims.

The year 2002 saw the launch of the Q TRAP[®] LC-MS-MS system (Figure 4), a first-ever union of triple quadrupole and ion trap technologies, which re-

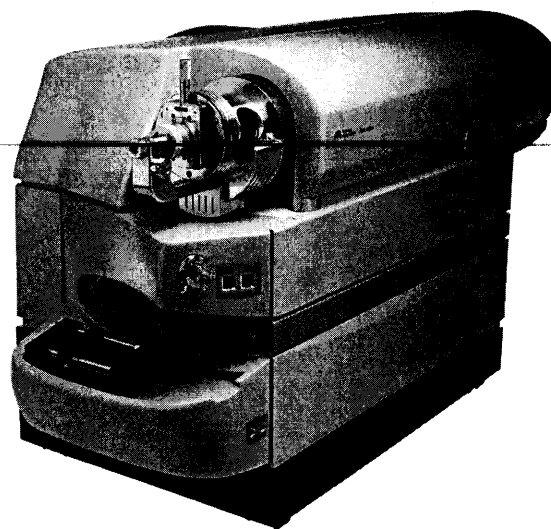


Figure 4 Q TRAP LC-MS-MS system.

searchers continue to use to identify proteins and peptides in proteomics research and small-molecule drug metabolites in therapeutic development.

In 2002, **Applied Biosystems** advanced the state-of-the-art of forensic DNA analysis, this time by launching AmpFLSTR Identifiler®, a single-amplification STR-based product that is rapidly becoming the global standard in forensic DNA analysis. Also in 2002, the company introduced custom TaqMan assays for gene expression and genotyping applications that have enabled scientists to detect any of the millions of single-nucleotide polymorphisms (SNPs) within the human genome. Scientists were now able to select from sets of hundreds of thousands of predesigned TaqMan primers and probes that covered the entire human genome to perform specific gene expression studies. That same year, **Applied Biosystems** introduced the 3730xl DNA analyzer, quadrupling the sequencing production capacity of researchers. Now, researchers were able to sequence up to two million bases per day, while dramatically reducing the cost per analysis and improving data quality. Together, the company's DNA analyzers and reagents have been used to identify 30,000 human genes and discover more than 10 million-plus unique SNPs.

In 2003, Catherine Burzik joined the **Applied Biosystems** management team, coming to the company from **Ortho-Clinical Diagnostics, A Johnson & Johnson Co.**, (Raritan, NJ). That year, a combination of **Applied Biosystems** DNA analyzers, real-time PCR systems, and protein identification systems were used by several groups of researchers around the world to sequence the Severe Acute Respiratory Syndrome (SARS) virus, and a short time later for clinical research leading to the development of diagnostic tests for the disease.

In 2004, the company took a leadership role in developing tools for biosecurity applications. At that time, the company established a collaboration with **Cepheid Corp.** (Sunnyvale, CA) in which TaqMan assay chemistry is now used to detect anthrax contamination of materials handled by the U.S. Postal Services.

In 2005, **Applied Biosystems/MDS SCIEX** responded to an increasing demand for the use of mass spectrometry systems in the food-and-beverage, environmental, forensic, clinical research, and pharmaceutical analysis markets. The company began commercial sales of several different mass spectrometry instruments, including the API 5000 LC-MS-MS system for small-molecule quantitation in pharma-

ceutical drug development, 4800 MALDI TOF/TOF analyzer, 3200 Q TRAP LC-MS-MS system, and API 3200 LC-MS-MS system.

At the close of 2005, **Applied Biosystems** reached an agreement to acquire the Research Products Division of **Ambion Inc.**, The RNA Company® (Austin, TX). A leader in the field of RNA, RNA interference (RNAi), and gene expression reagents, **Ambion** supplies RNA-based reagents for life science research and drug development.

Ever dedicated to serving the research customer, **Applied Biosystems** is now expanding to serve the clinical continuum, as the discoveries of basic science move toward the bedside. The company recently announced the intention to develop, register, and sell clinical diagnostic instruments to diagnostic laboratories and to help research customers take markers they discover through the clinical continuum in partnership with **Celera Genomics**, **Applied Biosystems'** sister business within **Applera Corp.** In addition, **Applied Biosystems** is applying its technologies to infectious disease detection. For example, collaborating with World Health Organization laboratories in Hong Kong and Australia, the company has developed assays to detect and sequence the Avian flu strain H5N1. The assays and the large installed base of the company's real-time PCR and DNA sequencing systems around the world offer an early warning system for the lethal virus.

According to Ms. Burzik, "The tools we develop are used for a diverse range of applications—to discover genes and proteins that are tied to diseases, to discover polymorphisms that may affect drug safety and efficacy, to measure drug metabolism, to provide early detection of dangerous pathogens, and to provide overwhelming evidence of guilt or innocence in serious crimes. And this isn't even a complete list. There are very few companies with the broad base of opportunities we have here for creating products that change lives."

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